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MISMATCH REPAIR AND P53 STATUS IN ENDOMETROID TYPE OF ENDOMETRIAL CARCINOMA, ASSOCIATION WITH CLINICOPATHOLOGICAL PARAMETERS IN IRAQI PATIENTS

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ABSTRACT

Background: Endometrial carcinoma is a common gynecological cancer and represents a major cause of morbidity and mortality among women.

Research Objectives

- Prevalence of MMR and P53 among Iraqi patients.
- Clinicopathological correlation.

Material and Methods: Cross sectional analytical study of surgically treated women with endometroid type of endometrial carcinoma. Statistical analysis was performed using IBM SPSS Statistics version 23. Continuous variables were summarized as mean ± standard deviation (SD) for the overall study population and as median with interquartile range (IQR) for group comparisons. **Result:** No statistically significant associations were observed between MMR status and other clinical and pathological variables ($p > 0.05$).No statistically significant associations were identified between p53 expression status and any of the studied clinicopathological variables ($p > 0.05$). **Conclusion:** MMR deficiency was identified in a substantial proportion of Iraqi patients, with MLH1/PMS2 co-loss being the predominant pattern. whereas aberrant p53 expression showed no significant association with the clinicopathological parameters examined. These findings provide preliminary molecular data on endometrioid endometrial carcinoma in the Iraqi population and support further investigation of MMR and p53 abnormalities in larger studies.

KEYWORDS: Endometroid endometrial carcinoma, mismatch repair proteins, MLH1. PMS2, P53.

INTRODUCTION

Endometrial carcinoma is the most common gynaecological malignancy in high- and middle-income countries and represents a major cause of cancer-related morbidity and mortality among women worldwide.[1] Endometrioid endometrial carcinoma is the most common histological subtype and is generally associated with estrogen-related pathogenesis and a more favorable clinical outcome than many non-endometrioid histological subtypes.[2]

Historically, endometrial carcinomas were classified according to Bokhman's dualistic model into Type I and Type II tumors based on epidemiological, clinical, pathological, and endocrine characteristics. Type I tumors were considered more common, typically associated with prolonged unopposed estrogenic stimulation, and predominantly composed of low-grade endometrioid carcinomas. In contrast, Type II tumors were characterized by more aggressive clinical behavior and traditionally included high-grade endometrioid carcinoma, serous carcinoma, clear cell carcinoma, undifferentiated carcinoma, and carcinosarcoma.[3-5] Although this model provided a useful framework for understanding endometrial carcinogenesis, it does not adequately reflect the substantial biological and molecular heterogeneity now recognized within endometrial carcinoma.

Despite advances in diagnosis and treatment, considerable heterogeneity exists among patients with endometrial carcinoma with respect to tumor behaviour, response to therapy, recurrence risk, and prognosis. Importantly, tumors with similar histological appearances may exhibit markedly different molecular profiles and clinical outcomes, highlighting the need for reliable molecular biomarkers that complement conventional clinicopathological assessment.[5,6]

Traditionally, prognostic assessment of endometrial carcinoma has relied on parameters such as histological type, tumor grade, depth of myometrial invasion, lymphovascular space invasion (LVSI), cervical stromal involvement, lymph node status, and FIGO stage. Although these parameters remain essential for patient management, morphological classification alone does not fully account for the biological diversity of endometrial carcinoma. Consequently, increasing attention has been directed toward molecular classification systems that provide additional prognostic and predictive information and facilitate more individualized risk stratification.[5,7]

A major advance in understanding the molecular pathogenesis of endometrial carcinoma was achieved by The Cancer Genome Atlas (TCGA) Research Network in 2013. Through comprehensive genomic, transcriptomic, and proteomic analysis, TCGA identified four distinct molecular categories: POLE-ultramutated, microsatellite instability (MSI)-hypermutated, copy-number-low, and copy-number-high tumors.[8] Subsequently, clinically applicable surrogate molecular classification systems were developed, allowing tumors to be categorized as POLE-mutated (POLEmut), mismatch repair-deficient (MMRd), p53-abnormal (p53abn), or no specific molecular profile (NSMP). These molecular groups have distinct prognostic characteristics and have increasingly been incorporated into contemporary risk-stratification systems and the 2023 FIGO staging system.[5,7]

The DNA mismatch repair (MMR) system is an essential cellular mechanism responsible for maintaining genomic stability through the recognition and correction of nucleotide mismatches and insertion-deletion errors arising during DNA replication. The principal MMR proteins evaluated in routine pathological practice are mutL homolog 1 (MLH1), postmeiotic segregation increased 2 (PMS2), mutS homolog 2 (MSH2), and mutS homolog 6 (MSH6). Functional loss of the MMR pathway results in mismatch repair deficiency and frequently leads to microsatellite instability, promoting the accumulation of somatic mutations and contributing to tumorigenesis.[9]

Immunohistochemical assessment of MLH1, PMS2, MSH2, and MSH6 expression provides a practical and widely available method for identifying MMR-deficient endometrial carcinomas and demonstrates good diagnostic performance as a surrogate for molecular MSI testing.[10] Loss of nuclear expression of one or more MMR proteins in tumor cells, in the presence of appropriate internal positive controls, supports the presence of MMR deficiency.

Mismatch repair deficiency occurs in a substantial proportion of endometrial carcinomas, including endometrioid carcinomas.[11] MMR deficiency may result from sporadic alterations, most commonly MLH1 promoter hypermethylation, or from germline pathogenic variants involving MMR pathway genes in patients with Lynch syndrome.[9] Accordingly, assessment of MMR status has clinical implications extending beyond tumor classification and prognosis, as it can facilitate the identification of patients who may require further evaluation for Lynch syndrome and can also provide predictive information relevant to immune checkpoint inhibitor therapy.[12]

Several studies have investigated the relationship between MMR status and clinicopathological characteristics of endometrial carcinoma. MMR-deficient tumors have been associated with distinct clinicopathological features, including differences in patient age, tumor grade, histological characteristics, and stage at diagnosis, although the reported associations and prognostic significance vary among studies and patient populations.[11,13] These observations support the concept that MMR status represents an important biological characteristic of endometrial carcinoma rather than merely a diagnostic marker.

The clinical relevance of MMR deficiency has become particularly important with the development of immune checkpoint inhibitor therapy. MMR-deficient and MSI-high tumors exhibit increased mutational burden and may generate enhanced tumor-associated neoantigens, providing a biological basis for their susceptibility to immune checkpoint blockade. Consequently, determination of MMR/MSI status has become an important biomarker for identifying patients who may benefit from immune checkpoint inhibitor therapy, further supporting the incorporation of routine MMR assessment into contemporary diagnostic practice.[12,14]

In addition to MMR status, immunohistochemical evaluation of p53 represents an important component of the molecular classification of endometrial carcinoma. Abnormal p53 immunohistochemical expression serves as a reliable surrogate for underlying TP53 alterations when appropriately interpreted and is used to identify the p53-abnormal molecular subgroup, which is generally associated with adverse biological behavior and prognosis.[5,15] Assessment of MMR proteins together with p53 immunohistochemistry therefore provides valuable information regarding tumor biology and contributes to practical molecular classification and prognostic stratification, particularly when incorporated into molecular classification algorithms such as the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE).[16]

Despite the increasing clinical importance of molecular classification, data regarding the prevalence and clinicopathological significance of MMR deficiency among Iraqi patients with endometrioid endometrial carcinoma remain limited. Differences in genetic background, environmental exposures, and population characteristics may influence the molecular and clinicopathological profiles of these tumors. Evaluation of MMR status within the Iraqi population may therefore provide valuable local data and contribute to a better understanding of the biological characteristics of endometrioid endometrial carcinoma in this population.

Therefore, the present study aims to assess mismatch repair protein expression in endometrioid endometrial carcinoma among Iraqi patients and to determine the frequency of MMR deficiency and its association with selected clinicopathological parameters. In addition, p53 immunohistochemical expression will be evaluated to further characterize the molecular features of these tumors and explore its relationship with MMR status and clinicopathological characteristics.

MATERIAL AND METHOD

The present study is a cross sectional analytical study conducted to estimate the prevalence of dMMR and P53 mutation among surgically treated patients in Iraqi hospitals and to assess the association between MMR and P53 status and patients age, tumor size, tumor grade, percent of myometrium invasion, uterine serosal involvement, lower uterine segment involvement, cervical stroma involvement, other tissue involvement, margin status, presence of adenomyosis, lymphovascular invasion and pathological tumor stage.

The study was conducted at the department of pathology, the national center of teaching laboratories, medical city, Baghdad, Iraq, during the period from December/2025 to June/2026.

All patients underwent total hysterectomy and bilateral salpingo-oophorectomy as part of the standard surgery.

The patients were staged according to the American joint committee on cancer (AJCC) 8th edition.

The study included 53 female patients diagnosed with endometroid endometrial carcinoma who underwent surgical resection, their age range from 29 to 77 years old.

Patients inclusion criteria

- Women with histologically confirmed endometroid endometrial carcinoma on hysterectomy specimen
- Available representative formalin fixed parffin embedded tumor tissue and original pathology report.
- Adequate clincal records for key variables.

Patients exclusion criteria

- Non endometroid tumor type (serous, clear cell, carcinosarcoma, etc).
- Insufficient tumor tissue for IHC.
- Prior neoadjuvant therapy that could alter IHC staining.

The patients were selected after reviewing H&E slides, choose blocks with viable invasive tumor, and avoiding extensive necrosis.

Representative tissue specimens were fixed in 10% neutral buffered formalin for 8 to 24h. According to the requirements of pathological technical specifications, sampling, dehydration, and embedding into paraffin block. Formalin-fixed, paraffin-embedded (FFPE) endometrial cancer blocks, which had high-quality tissue morphology, were used to prepare 4 μm sections on positively charged glass slides, routinely processed, and embedded in paraffin.

Immunohistochemical staining was performed using antibodies against (MLH1, PMS2, MSH2, MSH6) and (P53).

These antibodies have been optimized for specific incubation times, but the user must validate results obtained with this reagent. The effect of varying time and temperature of the antigen retrieval (cell conditioning) and antibody incubation from the recommended staining may result in sub-optimal staining and false deficient and false proficient results. Any deviation from recommended test procedures may invalidate expected results. Appropriate controls must be employed and documented. The tissue slices were deparaffinized, antigen retrieval was performed using a reaction buffer containing 0.3% carrier protein, and endogenous peroxidase was blocked using a pre-primary peroxidase inhibitor. Subsequently, tissue slices were incubated with primary antibodies. Finally, counterstaining was performed using hematoxylin, and post-counterstaining was performed by bluing for 4 min.

Each of the stained preparations was examined by two specialist histopathologists. They detected staining in the nuclei of tumor epithelial cells compared with the positive staining of stromal cells and lymphocytes as positive internal controls and the positive staining of normal appendix epithelial cells and lymphocytes of the subepithelial area as positive external controls.

The preparations were considered positive if tumor cells showed immunoreactivity that was equal to or stronger than that of positive controls and negative if tumor cells completely lost immunoreactivity. MMR proficiency was defined as positive IHC staining of all four proteins [MutL homolog 1 (MLH1), MutS homolog 2, MutS homolog 6 and PMS1 homolog 2 (PMS2)]. If at least one of them showed negative IHC staining, this was

interpreted as mismatch repair protein deficiency (dMMR).

P53 is considered wild type (normal) if the staining was scattered nuclear positive staining, or it considered as mutant if staining show either diffuse strong nuclear staining or complete absence of staining.

The clinical and pathological information were obtained from patients records and pathology reports.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 23. Continuous variables were summarized as mean ± standard deviation (SD) for the overall study population and as median with interquartile range (IQR) for group comparisons. The Mann–Whitney U test was used to compare continuous variables between two independent groups (pMMR vs. dMMR and p53 wild-type vs. mutant). Categorical variables were summarized as frequencies and percentages, and Fisher's exact test was used to assess associations between categorical clinicopathological variables and MMR or p53 status.

RESULTS

A total of 53 surgically treated Iraqi patients diagnosed with endometrioid endometrial carcinoma were analyzed. The mean age of the participants was 59.1 ± 9.6 years (range: 29–77 years). The mean maximum tumor dimension was 4.08 ± 1.52 cm.

1. Prevalence and Expression Profiles of dMMR

Mismatch repair deficiency (dMMR) was identified in **12 out of 53 patients**, (**22.6%)** in the study.

-MLH1 / PMS2 Co-loss: 11 cases (91.7% of dMMR tumors) demonstrated concurrent loss of MLH1 and PMS2 nuclear expression.

-Isolated PMS2 Loss: 1 case (8.3% of dMMR tumors) exhibited isolated loss of PMS2 expression with intact MLH1.

-MSH2 / MSH6 Expression: Intact nuclear expression of MSH2 and MSH6 was preserved across all 53 tumor samples (100%).

2. Association Between MMR Status and Clinicopathological Variables

Table 1 summarizes the association between mismatch repair status (pMMR vs. dMMR) and patient age, maximum tumor dimension, histologic grade, depth of myometrial invasion, lymphovascular invasion (LVI), pathological tumor stage and other clinical and pathological features.

Table 1: Association Between MMR Status and Clinicopathological Variables.

Clinicopathological Variable	pMMR (n = 41)	dMMR (n = 12)	Statistical Test	p-value
Age (years), Median (IQR)	60.0 (54.0–65.0)	60.0 (51.5–64.0)	Mann–Whitney U	0.632
Tumor Max Dimension (cm), Median (IQR)	4.00 (3.00–5.00)	3.00 (2.75–4.00)	Mann–Whitney U	**0.044***
Histologic Grade • Grade 1 / Grade 2 • Grade 3	 36 (87.8%) 5 (12.2%)	 10 (83.3%) 2 (16.7%)	Fisher's Exact	0.650
Depth of Myometrial Invasion • < 50% (Superficial / None) • ≥ 50% (Deep)	 19 (46.3%) 22 (53.7%)	 8 (66.7%) 4 (33.3%)	Fisher's Exact	0.327
Lower Uterine Segment Involvement • Uninvolved • Involved	 22 (53.7%) 19 (46.3%)	 11(91.7%) 1 (8.3%)	Fisher's Exact	**0.020***
Cervical Stroma Involvement • Uninvolved • Involved	 33 (80.5%) 8 (19.5%)	 10 (83.3%) 2 (16.7%)	Fisher's Exact	1.000
Uterine Serosal Involvement • Absent • Present	 35 (85.4%) 6 (14.6%)	 11 (91.7%) 1 (8.3%)	Fisher's Exact	0.679
Other Tissue / Adnexal Involvement • Absent • Present	 39 (95.1%) 2 (4.9%)	 11 (91.7%) 1 (8.3%)	Fisher's Exact	0.534
Surgical Margin Status • Free • involved	 40 (97.6%) 1 (2.4%)	 12 (91.7%) 0 (0%)	Fisher's Exact	1.000
Presence of Adenomyosis • Absent • Present	 33 (80.5%) 8 (19.5%)	 9 (75.0%) 3 (25.0%)	Fisher's Exact	0.697

Lymphovascular Invasion (LVI) • Not Identified • Identified	 31 (75.6%) 10 (24.4%)	 10 (83.3%) 2 (16.7%)	Fisher's Exact	0.711
Pathological tumor stage • Stage I • Stage II – IV	 31 (75.6%) 10 (24.4%)	 9 (75.0%) 3 (25.0%)	Fisher's Exact	1.000

Maximum tumor diameter was significantly smaller in dMMR tumors compared to pMMR tumors (median 3.00 cm [IQR: 2.75-4.00] vs. 4.00cm; [IQR: 3.00-5.00] respectively) Mann-Whitney U = 152.50, Z = -2.016, p = 0.044).

A statistically significant association was observed between MMR status and lower uterine segment involvement. Lower uterine segment involvement was identified in 19 of 41 pMMR tumors (46.3%), compared with 1 of 12 dMMR tumors (8.3%). Conversely, the lower uterine segment was uninvolved in 53.7% of pMMR tumors and 91.7% of dMMR tumors.

No statistically significant associations were observed between MMR status and other clinical and pathological variables ($p > 0.05$).

3. Association Between p53 Expression and Clinicopathological Variables

Mutant p53 expression was detected in **23 out of 53 cases (43.4%)**. Table 2 details the comparison between p53 wild-type and p53 mutant tumors across clinical and pathological features.

Table 2: Association Between p53 Expression and Clinicopathological Variables.

Clinicopathological Variable	p53 Wild-type (n = 30)	p53 Mutant (n = 23)	Statistical Test	p-value
Age (years), Median (IQR)	60.0 (52.5–64.0)	60.0 (55.5–67.0)	Mann–Whitney U	0.332
Tumor Max Dimension (cm), Median (IQR)	4.00 (3.00–5.38)	4.00 (3.00–4.25)	Mann–Whitney U	0.402
Histologic Grade • Grade 1 / Grade 2 • Grade 3	 28 (93.3%) 2 (6.7%)	 18 (78.3%) 5 (21.7%)	Fisher's Exact	0.218
Depth of Myometrial Invasion • < 50% (Superficial / None) • ≥ 50% (Deep)	 15 (50.0%) 15 (50.0%)	 12 (52.2%) 11 (47.8%)	Fisher's Exact	1.000
Lower Uterine Segment Involvement • Uninvolved • Involved	 17 (56.7%) 13 (43.3%)	 16 (69.6%) 7 (30.4%)	Fisher's Exact	0.400
Cervical Stroma Involvement • Uninvolved • Involved	 24 (80.0%) 6 (20.0%)	 19 (82.6%) 4 (17.4%)	Fisher's Exact	1.000
Uterine Serosal Involvement • Absent • Present	 28 (93.3%) 2 (6.7%)	 21 (91.3%) 2 (8.7%)	Fisher's Exact	1.000
Other Tissue / Adnexal Involvement • Absent • Present	 28 (93.3%) 2 (6.7%)	 22 (95.7%) 1 (4.3%)	Fisher's Exact	1.000
Surgical Margin Status • Negative (Free) • Positive	 28 (93.3%) 2 (6.7%)	 22 (95.7%) 1 (4.3%)	Fisher's Exact	1.000

(Involved)				
Presence of Adenomyosis • Absent • Present	21 (70.0%) 9 (30.0%)	16 (69.6%) 7 (30.4%)	Fisher's Exact	1.000
Lymphovascular Invasion (LVI) • Not Identified • Identified	21 (70.0%) 9 (30.0%)	20 (87.0%) 3 (13.0%)	Fisher's Exact	0.193
Pathological tumor Stage • Stage I • Stage II – IV	22 (73.3%) 8 (26.7%)	18 (78.3%) 5 (21.7%)	Fisher's Exact	0.756

No statistically significant associations were identified between p53 expression status and any of the studied clinicopathological variables ($p > 0.05$).

DISCUSSION

In this study, we evaluated mismatch repair (MMR) protein expression and p53 status in 53 Iraqi patients who underwent surgical resection for endometrioid endometrial carcinoma (EEC). To our knowledge, this study provides preliminary data on the molecular and clinicopathological characteristics of EEC in an Iraqi population, which remains relatively underrepresented in the published literature.[16,17]

Prevalence and Patterns of dMMR

Mismatch repair deficiency (dMMR) was identified in 22.6% of patients in the current study. This prevalence of (dMMR) tumor in endometrioid endometrial carcinoma is consistent with previously reported estimates for dMMR in EEC, which generally range from approximately 20% to 30%.[18,19] The similarity between our findings and international data suggests that dMMR represents a substantial molecular subgroup of EEC.

Among the dMMR tumors, 91.7% (11/12) demonstrated concurrent loss of MLH1 and PMS2 expression, while isolated PMS2 loss was observed in one case (8.3%). The predominance of MLH1/PMS2 co-loss is consistent with the known pattern of MMR deficiency in endometrial carcinoma, in which loss of MLH1 expression is frequently associated with loss of its heterodimer partner PMS2.[20,21]

Although MLH1/PMS2 co-loss is commonly associated with somatic MLH1 promoter hypermethylation, this mechanism cannot be confirmed in the present study because MLH1 promoter methylation testing was not performed. Similarly, isolated PMS2 loss may occur in the setting of germline or somatic alterations involving PMS2 and requires further molecular evaluation for definitive classification.[22]

No loss of MSH2 or MSH6 expression was observed in this study. Although abnormalities involving these proteins may be associated with Lynch syndrome.[23] Larger studies incorporating germline testing and/or appropriate molecular investigations are required to determine the contribution of Lynch syndrome-associated alterations.

Clinicopathological associations of MMR Status

In this study, dMMR tumors displayed a significantly smaller median maximum diameter compared to pMMR tumors (3.00 cm vs. 4.00 cm, $p = 0.044$). While classical literature often links dMMR to larger tumor burdens driven by hypermutation and rapid cellular proliferation[24,25], our finding of smaller tumor size in dMMR cases aligns with recent observations suggesting that dMMR tumors may exhibit indolent early growth kinetics or prompt earlier clinical detection due to localized inflammatory microenvironments.[26,27]

Additionally, lower uterine segment involvement was observed less frequently in dMMR tumors than in pMMR tumors (8.3% vs. 46.3%, $p = 0.020$). Anatomical predilection for the lower uterine segment has been historically highlighted as a hallmark feature in Lynch syndrome-associated cases.[28,29] In contrast, in unselected or predominantly sporadic cohorts, dMMR is most commonly driven by somatic epigenetic *MLH1* promoter hypermethylation arising within the main uterine corpus.[10, 14] The high rate of LUS preservation (91.7%) in our dMMR cases alongside the predominance of MLH1/PMS2 co-loss (91.7%) may indirectly suggest a higher proportion of sporadic epigenetic dMMR rather than germline-driven disease.[25, 29]

No statistically significant associations were identified between MMR status and age, histologic grade, depth of myometrial invasion, cervical stromal involvement, uterine serosal involvement, other tissue/adnexal involvement, surgical margin status, adenomyosis, LVI, or pathological tumor stage ($p > 0.05$), While several large-scale studies (such as the NRG/GOG0210 trial) reported that dMMR endometrial tumors are significantly associated with more aggressive baseline pathological features including high histologic grade, deep myometrial invasion, and frequent LVI, compared to pMMR tumors[30] However, other recent single-center and cohort studies align with our results, reporting no statistically significant differences in these standard

morphological parameters between dMMR and pMMR groups.[25,31]

P53 Expression Profile

Mutant p53 expression was identified in 43.4% (23/53) of tumors. This proportion appears relatively high compared with the frequency generally reported in predominantly low-grade endometrioid carcinomas, although p53 abnormalities are substantially more frequent in high-grade and serous endometrial carcinomas.[32-34] The proportion observed in our study may partly reflect the histological composition of the study population, case selection, or referral patterns.

No significant association was found between p53 status and any of the investigated clinicopathological variables. These findings are in line with previous reports showing no significant relationship between p53 expression and age, histological grade, stage, or depth of myometrial invasion.[35,36] In contrast, other studies have reported significant associations between abnormal p53 expression and adverse pathological features, including advanced stage, higher grade, deep myometrial invasion, and lymphovascular invasion.[37,38] The differences among studies may be related to variations in sample size, patient characteristics, and study population.

Overall, the present findings indicate that p53 expression was not significantly associated with the clinicopathological parameters examined in this study.

Finally, the relatively small sample size (n = 53) may have limited the statistical power to detect clinicopathological associations, representing a limitation of the present study. Therefore, further large-scale studies are recommended to deepen the understanding and clarify the clinical impact of these molecular markers in Iraqi patients with endometrioid endometrial carcinoma.

Limitation

The relatively small sample size (n = 53) should be considered when interpreting the findings of the present study. Further studies involving larger cohorts would be valuable to confirm the observed associations and provide a broader understanding of the molecular and clinicopathological characteristics of endometrioid endometrial carcinoma in the Iraqi population.

CONCLUSION

This study provides preliminary data on MMR and p53 expression in Iraqi patients with endometrioid endometrial carcinoma. MMR deficiency was identified in 22.6% of cases, with MLH1/PMS2 co-loss representing the predominant pattern. dMMR was significantly associated with smaller tumor size and less frequent lower uterine segment involvement, while no significant associations were observed with most other clinicopathological characteristics. Aberrant p53 expression was observed in 43.4% of cases and was not significantly associated with the clinicopathological parameters examined. Overall, these findings add to the limited molecular data available on endometrioid endometrial carcinoma in the Iraqi population and describe the observed MMR and p53 expression patterns in the studied patients.

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